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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,754	09/01/2006	Yoshiko Yoshiyama	2006_1459A	3249

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EXAMINER	
LEE, JAE W	

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
03/12/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/591,754	YOSHIYAMA ET AL.	
	Examiner	Art Unit	
	JAE W. LEE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,8,9,12 and 21-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,8,9,12 and 21-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application status

In response to the previous Office action, a non-Final rejection (mailed on 08/17/2009), Applicants filed a response and amendment received on 12/17/2009. Said amendment canceled Claims 3, 6, 7, 10, 11, 13-20, amended Claims 1, 8 and 9, and added Claims 21-31. Thus, Claims 1, 2, 4, 5, 8, 9, 12 and 21-31 are at issue and present for examination.

Applicants' arguments filed on 12/17/2009, have been fully considered, and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Objections

The previous objection of Claims 3 and 11 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, is withdrawn because Applicants have canceled these claims.

The previous objection of Claim 13 for being duplicative of claim 4 is withdrawn because Applicants have canceled these claims.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

All of the previous rejections of Claims 1-5, 8-13 and 18-20 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, are withdrawn by virtue of Applicants' amendment.

Claim Rejections - 35 USC § 102

The previous rejection of Claims 1, 10 and 20 under 35 U.S.C. 102(b) as being anticipated by Gonzalez et al. (A Novel Interaction between Perlecan Protein Core and Progranulin, The Journal of Biological Chemistry, Vol. 278, No. 40, Issue of October 3, pp. 38113–38116, 2003) is withdrawn by virtue of Applicants' amendment.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The previous rejection of Claims 1-5, 8, 9, 11-13, 18 and 19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Madin et al. (A highly efficient and

robust cell-free protein synthesis system prepared from wheat embryos: Plants apparently contain a suicide system directed at ribosomes, PNAS, January 18, 2000, Vol. 97, No. 2, pp: 559–564) in view of Zacharias et al. (Recombinant-protein solubility screening using the EasyXpress in vitro translation system, QIAGEN News 2004 e6, Retrieved from the Internet <URL:www1.qiagen.com/literature/qiagennews/weeklyArticle/04_02/e6/default.aspx>) is withdrawn in favor of a new rejection as shown below.

Claims 1, 2, 4, 5, 8, 9, 12 and 21-31are rejected under 35 U.S.C. § 103(a) as being unpatentable over Greene et al. (THE JOURNAL OF BIOLOGICAL CHEMISTRY Vol. 278, No. 9, Issue of February 28, pp. 7617–7623, 2003), in view of Zacharias et al. (Recombinant-protein solubility screening using the EasyXpress in vitro translation system, QIAGEN News 2004 e6, Retrieved from the Internet URL:www1.qiagen.com/literature/qiagennews/weeklyArticle/04_02/e6/default.aspx - cited on previous PTO-892), Madin et al. (A highly efficient and robust cell-free protein synthesis system prepared from wheat embryos: Plants apparently contain a suicide system directed at ribosomes, PNAS, January 18, 2000, Vol. 97, No. 2, pp: 559–564 – cited on previous PTO-892), KSR International Co. v. Teleflex Inc., 550 U.S.--, 82 USPQ2d 1385 (2007) and an evidentiary reference of Kimple et al. (Overview of affinity tags for protein purification, Curr Protoc Protein Sci., Sept. 2004, Chapter 9: Unit 9.9).

The instant claims are drawn to a method of removing substances from a cell extract that bind an affinity support but do not contribute to protein synthesis,

comprising: a) providing a cell extract capable of synthesis of a protein and an affinity support capable of binding to the protein, and b) contacting the cell extract prior to synthesis of the protein with the affinity support and thereby removing substances bound to the affinity support from the cell extract, and wherein removal of substances bound to the affinity support does not impair the protein synthetic activity of the cell extract.

Greene et al. teach a method of performing immunoprecipitation comprising 1) pre-clearing the cell extract made from Rat embryo fibroblast cells with a first affinity support, i.e., protein-A-sepharose beads, 2) removing substances bound to the first affinity support, and 3) contacting the cell extract with a second affinity support, i.e., fresh protein-A-sepharose beads (see page 7618, right column, under "Immunoprecipitation").

Greene et al. do not teach a method of protein production.

Zacharias et al. teach a method of producing a protein via cell-free protein synthesis comprising [i] synthesizing mRNA which encodes the protein of interest with an affinity tag, i.e., His-6 tag, [ii] using the cell-free *in vitro* translation reactions to express said protein, and [iii] contacting the reactions with an affinity support, i.e., Ni-NTA Magnetic Agarose Beads, which has an affinity to the His-6 tagged protein of interest, [iv] removing the said affinity support, thereby purifying the protein of interest (see pages 1-5). Since this is a commercially successful method of producing a protein of interest utilizing the Ni-NTA Magnetic Agarose Beads, i.e., a nickel immobilized

support, it is an inherent characteristic of the Ni-NTA Magnetic Agarose Beads not to impair the protein synthesis of the cell-free *in vitro* translation reactions.

Madin et al. teach a method of producing a protein, i.e., DHFR via cell-free protein synthesis, comprising synthesizing said protein using cell-free wheat germ cell extract (see page 560-561 under "Materials and Methods").

It would have been obvious to one of ordinary skill in the art to make and use a method of producing a protein of interest via cell-free protein synthesis, comprising [1] pre-clearing the cell extract with a first affinity support, [2] removing substances bound to the first affinity support, [3] contacting the cell extract with a fresh affinity support, thereby removing any substances that bind the affinity support, [4] synthesizing mRNA which encodes the protein of interest with an affinity tag, i.e., His-6 tag, [5] using the cell-free *in vitro* translation reactions to express said protein, and [6] contacting the reactions with the affinity support, i.e., Ni-NTA Magnetic Agarose Beads, which has an affinity to the His-6 tagged protein of interest, and [7] removing the said affinity support, thereby purifying the protein of interest, optionally wherein said cell extract is a wheat germ extract, as taught by Greene et al., Zacharias et al. and Madin et al. It is noted by the Examiner that as evidenced in Kimple et al. the metal ion affinity support such as Ni-NTA Magnetic Agarose Beads and a glutathione immobilized support are art-recognized equivalents (see under "Polyhistidine" and "Glutathione S-Transferase"). One would have been motivated to "pre-clear" cell extracts with an affinity support prior to actual affinity based purification of a protein of interest, i.e., (IMAC: immobilized metal affinity chromatography) because such would remove any substances which non-specifically

bind to the affinity support, thereby improving the specific interaction between the affinity tag and the affinity support, i.e., His-6 tag with Ni-NTA Magnetic Agarose Beads, respectively, and increasing the yield of the protein of interest. Furthermore, one would have been motivated to replace the cell-free *in vitro* translation kit taught by Zacharias et al. with the cell-free wheat germ cell extract taught by Madin et al. because Madin et al. teach that there are numerous advantages to use the wheat germ cell-free systems, i.e., [a] low cost, [b] easy availability in large amounts, [c] low endogenous incorporation, [d] the capacity to synthesize high-molecular-weight proteins, and [e] more suitable for the expression of eukaryotic proteins (see page 559, right column, 2nd paragraph). In addition, there is a high expectation of success because [A] methods for pre-clearing cell extracts with an affinity support, [B] use of wheat germ cell extracts in the cell-free protein synthesis, and [C] affinity tags/affinity support for the purification of recombinant proteins have been rampantly practiced in the field of recombinant protein production and affinity based protein purification prior to the filing of the instant application. As discussed in KSR International Co. v. Teleflex Inc., 550 U.S.--, 82 USPQ2d 1385 (2007), it is considered obvious to combine prior art elements known to be used in equivalent fields of endeavor together into a single combination. The combined teachings of the references clearly show that the methods of "pre-clearing" cell extracts with an affinity support as taught by Greene et al., methods of using commercially available cell-free protein synthesis kit as taught by Zacharias et al., and the method of using wheat germ extracts for cell-free protein synthesis as taught by Madin et al. were known to be used in equivalent fields of endeavor, i.e., in the field of

cell-free protein synthesis and affinity based protein purification; thus, it is considered obvious to combine them together. Therefore, Claims 1, 2, 4, 5, 8, 9, 12 and 21-31 are *prima facie* obvious over the combined teachings of the prior art.

Conclusion

Claims 1, 2, 4, 5, 8, 9, 12 and 21-31 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on M-F between 9:00-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JAE W LEE/
Examiner, Art Unit 1656

/SUZANNE M. NOAKES/
Primary Examiner, Art Unit 1656